entitled **Version with Markings to Show Changes Made**. For the Examiner's convenience, a clean copy of all pending claims is attached, entitled "**Appendix A: Pending Claims**".

Claim Status

Claims 36-39, 45-47, 49-50, and 52-53 are pending in the application. Claims 36, 45, and 52 are amended herein, and claims 40-44, 48, and 51 cancelled. Support for the above claim amendments can be found in the originally filed claims. Claims 36-53 stand rejected. Further, the drawings stand objected to.

Drawings

The drawings stand objected to under 37 C.F.R. §1.83(a).

The Examiner suggests the "detection electrode", the "self-assembled monolayer", and the "binding ligand" recited in claim 36 must be shown or the features cancelled from the claims. Applicants respectfully submit that the detection electrode is depicted in Figures 1A-D as reference numeral 35. The corresponding description can be found on page 2, line 7. As to the "self-assembled monolayer" and the "binding ligand", Applicants enclose a proposed Figure 2. Proposed Fig. 2 is a schematic cross-sectional view of detection electrode 35. Proposed Fig. 2 is supported by the specification at least by the paragraph beginning at page 43, line 16 and the paragraph beginning at page 57, line 17, which have been amended above to include reference to the Figure. The paragraph beginning at page 43, line 16 describes that an electrode comprises a self-assembled monolayer. Support for the structural depiction of SAM 100 in proposed Figure 2 is found at least on page 43, lines 18-19 which state that the molecules are oriented approximately parallel to each other and roughly perpendicular to the surface, as shown in proposed Figure 2. Support for the structural depiction of binding ligand 120 in proposed Figure 2 is found at least in the depiction 'Structure 17', and on page 69 lines 22-26 which clearly state that in one embodiment, binding ligands are covalently attached to the electrode via an insulator. "Insulator" was previously defined on page 53, lines 8-12 as one moiety making up the self-assembled monolayer. Therefore, Applicants submit that proposed Figure 2 adds no new matter, and should be entered. Applicants submit that the "detection electrode", the "self-assembled monolayer", and the "binding ligand" are now shown in the Figures, and the features accordingly remain in the claims.

The Examiner suggests the "filter" recited in claim 39 must be shown or the feature cancelled from the claims. Applicants accordingly enclose proposed drawing changes to Fig. 1B including filter 200 shown in two locations. Applicants submit support for the amendment to Figure 1B can be found in the paragraph beginning on page 11, line 22 stating that the filter may be between the cell lysis module and a subsequent module. The paragraph has been amended as above to include reference to Figure 1B. Thus, in Figure 1B the filter is placed between the sample handling well 40 and the detection module 30. A cell lysis module is one type of cell handling module, as noted on page 10 line 12. The lysis module is shown in Fig. 1B as reference number 200 and without structural detail. Applicants note that 37 C.F.R. §1.83(a) states that "conventional features disclosed in the description and claims, where their detailed illustration is not essential for a proper understanding of the invention, should be illustrated in the drawing in the form of a graphical drawing symbol or a labeled representation (e.g., a labeled rectangular box)". Accordingly, Applicants represent filter as a circle with a reference number. More detailed filter structures can be found in EP 0 637 998 B1, incorporated by reference into the specification at page 11, line 25. Applicants therefore submit that the amendment to Figure 1B introduces no new matter, and should be accepted. Further, Applicants submit that a "filter" feature is shown in the figures, and the feature accordingly remains in the claims. However, the inclusion of the filter 200 is optional, and its inclusion in Fig. 1B is not to be construed as limiting the scope ofthe invention in any way.

The Examiner stated that the "cell capture structure provided in said sample handling well" recited in claim 40; the cell separation structure provided in said sample handling well" recited in claim 42; the "electrophoretic microchannel and electrodes" recited in claim 43 should be shown in the figures or the feature(s) cancelled from the claims. Without admitting to the propriety of the rejection, Applicants have cancelled claims 40-44 in an effort to further prosecution.

The Examiner stated that all the structure recited in claim 45 needed to be shown or the features cancelled from the claims. Applicants respectfully submit that the structure recited in amended claim 45 is shown in Figure 1D which depicts "a reaction module formed in said support member" (see Fig. 1D and page 2, line 12), "wherein an additional microchannel connects the reaction module to said sample handling well" (see Fig 1D and page 2, line 8), "and a further microchannel connects the reaction well to said detection module." (see Fig. 1D and page 2, line 7). As is stated throughout the specification, Applicants note that Fig. 1D represents only one

embodiment of the configuration of wells, channels, and modules. Accordingly Applicants submit that the features should remain in the claims.

The Examiner states that "the electrical resistance heater positioned in said reaction module" recited in claim 47 must be shown in the figures or the feature cancelled from the claims. Applicants therefore submit amended Fig. 1D, displaying electrical resistance heater 250. Support for the feature is found at least in the paragraph beginning on page 38, line 16, which is amended as above to include a reference to heater 250. The heater is shown in Fig. 1D without structural detail. As above, Applicants note that 37 C.F.R. §1.83(a) does not require a detailed representation of conventional elements. Accordingly, Applicants represent heater 250 as a resistive trace with a reference number. More detailed heater structures can be found in, for example, U.S. Patent Numbers 5,498,392 and 5,587,128, incorporated by reference into the specification at page 38, line 19. Applicants therefore submit that the amendment to Figure 1D introduces no newmatter, and should be accepted. Further, Applicants submit that an "electrical resistance heater" feature is shown in the figures, and the feature accordingly remains in the claims. However, the inclusion of heater 250 is optional, and its inclusion in Fig. 1D is not to be construed as limiting the scope of the invention in any way.

The Examiner stated that the "resistance heater positioned in said sample handling module" recited in claim 48 must be shown or the feature cancelled from the claim. Without admitting the propriety of the rejection, and in the interests of furthering prosecution, Applicants have cancelled claim 48 without prejudice or disclaimer.

The Examiner stated that the "means for inducing flow" recited in claim 49 and the "pump" recited in claim 50 must be shown or the features cancelled from the claims. Applicants accordingly submit amended Fig. 1A. Amended Fig. 1A includes a depiction of two electrodes along a channel, collectively labeled as pump 260 comprising electrodes 261 and 262. Such a pump comprising electrodes along a channel is supported by the specification at least at the paragraph beginning on page 39, line 5. The paragraph beginning at page 39, line 5 has been amended to include a reference to the Figure. Accordingly, Applicants submit that the amendment to Fig. 1A introduces no new matter, and should be accepted. Further, Applicants submit that one embodiment of a 'pump' and 'means for inducing flow', as recited in claims 49 and 50, are shown in the figures, and

the features therefore remain in the claims. However, the inclusion of pump 260 is optional, and its inclusion in Fig. 1A is not to be construed as limiting the scope ofthe invention in any way.

The Examiner stated that the "means for holding said sample" recited in claim 51 and the "valve" recited in claim 52 must be shown or the features cancelled from the claims. Applicants refer to the enclosed amended Fig. 1A. Amended Fig. 1A contains pump 260, discussed above as well as valve 280, which is discussed here. As a preliminary matter, claim 51 has been cancelled. Applicants submit that support for the addition of valve 280 to Fig. 1A is supported at least in the paragraph beginning on page 40, line 28, which paragraph has been amended to include reference to valve 280. As discussed above, Applicants note that 37 C.F.R. §1.83(a) does not require a detailed representation of conventional elements. Accordingly, Applicants represent valve 280 as a circle with an X and a reference number. More detailed valve structures can be found in, for example, PCT US97/07880, incorporated by reference into the specification at page 40, line 31 and U.S. Patent Number 5,858,195, incorporated by reference into the specification at page 41, line 2. Applicants therefore submit that the amendment to Figure 1A introduces no new matter, and should be accepted. Further, Applicants submit that an embodiment of a "means for controlling flow of said sample" and a "valve" feature is shown in the figures, and the features accordingly remain in the claims. However, the inclusion of valve 280 is optional, and its inclusion in Fig. 1A is not to be construed as limiting the scope of the invention in any way.

In summary, Applicants submit that the proposed amended Figs. 1A, 1B, 1D, and 2 contain no new matter, are fully supported by the specification, and show the claimed features. Accordingly, Applicants respectfully request that the drawing amendments be accepted, and the objection to the drawings be withdrawn.

Claim Rejections - 35 U.S.C. §112

Claims 40-44 and 48 were rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Without admitting to the propriety of the rejection, Applicants have cancelled claims 40-44 and 48 without prejudice or disclaimer.

Claims 36-53 were rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. As a preliminary matter, Applicants note that claims 40-44 and 48 have been cancelled without prejudice or disclaimer. Support for the structural organization of the claimed elements is given above in the discussion of the figures. Applicants respectfully submit that the structural organization of the elements is fully supported at least by the above references to the specification. Further, with regard to the written description requirement of 35 U.S.C. § 112, first paragraph, Applicants wish to point out that it is well settled case law that the claimed subject matter need not be set forth "literally or *in haec verba*" in order for the specification to satisfy the written description requirement of 35 U.S.C. § 112, first paragraph (In re Lukach, 169 USPQ 795 (CCPA 1971) and Martin v. Johnson, 172 USPQ 391,395 (CCPA 1972)). All that is required for an adequate written description is that the specification "convey clearly to those skilled in the art, to whom it is addressed, in any way, the information that the applicant has invented the specific subject matter later claimed" (In re Wertheim, 191 USPQ 90, 97 (CCPA 1976)). In many cases, the structural organization of the elements is inherently understood, often well known in the art, and may be accomplished in a variety of ways. Numerous references are incorporated by reference into the specification, including those listed at page 1, lines 15-23 which demonstrate some known structural organizations of microfluidic elements.

Further, the Examiner states that some required elements, such as a counter electrode and fluid, are not described in the specification. Applicants submit that the application of a potential between a conjugated detection electrode and a reference electrode is discussed at least on page 102, lines 14-19, page 106, lines 16-25, page 106 lines 31-32, and page 110, lines 4-9. The applicants respectfully remind the Examiner that "a patent need not teach, and preferably omits, what is well known in the art". Spectra-Physics, Inc. v. Coherent, Inc., 2 USPQ 2d 1737 (Fed. Cir. 1987). Furthermore, the standard for 112 enablement is that one skilled in the art would be able to use the description of the invention to make and use the claimed invention. "An inventor need not, however, explain every detail since he is speaking to those skilled in the art". DeGeorge v. Bernier, 226 USPQ 758, 762 (Fed. Cir. 1985). In this case, one of skill in the art would appreciate the presence of both counter-electrodes and fluids, given the teachings in the specification and the state of the art.

If the Examiner does not agree, Applicants respectfully request further guidance as to which elements in the claims the Examiner finds are not supported per 35 U.S.C. §112. Accordingly, Applicants submit that the elements recited in claims 36-39, 45-47, and 49-53 are fully supported by the specification, and the 35 U.S.C §112, first paragraph, rejection should be withdrawn.

Claims 36-53 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 36-53 are rejected as being incomplete.

The Examiner states that the combination of elements recited as a "detection module" cannot perform the detection function; and that "all embodiments of the detector module require elements in addition to those recited in claim 36". As a preliminary matter, Applicants submit that all elements required to perform detection need not be specifically recited in claim 36; as noted by the Examiner, these elements may vary depending on the detection technique utilized. Again, the Examiner is respectfully reminded that the standard for 112 enablement is that one skilled in the art would be able to use the description of the invention to make and use the claimed invention. "An inventor need not, however, explain every detail since he is speaking to those skilled in the art". DeGeorge, supra. However, in the interests of furthering the prosecution, and without admitting the propriety of the rejection, the claim has been amended to recite a "detection well" comprising the "detection electrode".

The Examiner also rejected claim 51 as being indefinite. Without admitting the propriety of the rejection, claim 51 has been amended to recite "means for controlling flow of said sample". Accordingly, Applicants submit that claims 36-39, 45-47, and 49-53 particularly point out and distinctly claim the subject matter which applicant regards as the invention, and the 35 U.S.C. §112, second paragraph, rejection should be withdrawn.

Claim Rejections - 35 U.S.C. §102

Claims 36 and 42 were rejected under 35 U.S.C. §102(e) as being anticipated by Segal et al. (U.S. Patent Number 6,300,141 B1). As a preliminary matter, Applicants note that claim 42 has been cancelled.

Applicants submit that the Segal reference is not a proper prior art reference. The Segal reference has a filing date of March 2, 2000, and claims priority to Provisional Application No. 60/122,546, filed March 2, 1999. Enclosed is a declaration by the inventor, Jon F. Kayyem, submitted under 37 C.F.R. §1.131, referencing notes from a meeting dated prior to March 2, 1999. The declaration outlines that the invention was completed in this country prior to March 2, 1999.

Notes from a meeting prior to March 2, 1999 are attached as Exhibit 1. The notes indicate that microfluidics were discussed, and further that the combination of microfluidics and CMS technology was contemplated. As outlined in the enclosed declaration by Jon Kayyem, 'CMS technology' refers to electronic detection methods such as those outlined in U.S. Patent Nos. 6,096,273; 6,221,583; and, 6,232,062, and in U.S.S.N.s 08/873,597; and, 09/135,183, all filed prior to March 2, 1999. Microfluidic technology publicly available prior to March 2, 1999 included a solid support member, sample handling well, sample inlet port, and microchannels, as evidenced by Wilding et. al. U.S. Patent Number 5,304,487 issued April 19, 1994. Therefore, the note to combine CMS technology with microfluidics contained in Exhibit 1 demonstrates that the invention was made in this country prior to March 2, 1999. Accordingly, the Segal reference is not a proper prior art reference, and the Segal reference, along with the 35 U.S.C. §102(e) rejection of claim 36 over Segal, should be withdrawn.

CONCLUSION

Applicant submits that the claims are in condition for allowance, and early notification of such is earnestly solicited. The Examiner is invited to telephone the undersigned attorney in the event that further issues are identified that would preclude allowance of the claims.

Enclosed is our check to cover the cost of added claims not already paid for. While Applicant believes that no further fees are due at this time, the Commissioner is authorized to charge any fees that may be due as a result of filing this amendment, including additional claims fees not already paid for, or other fees that have not been separately paid, to Deposit Account 50-2319 (Order No.463037-00168 [A-67465/RFT/RMS/RMK]).

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Respectfully submitted,

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APPENDIX WITH MARKINGS SHOWING CHANGES MADE

In the Specification

The following paragraph was added after page 2, line 15:

Figure 2 depicts a cross-sectional schematic view of a detection electrode according to one embodiment of the present invention.

The paragraph beginning on page 11, line 22 was amended as follows:

The cell lysis module may also include, either internally or externally, a filtering module for the removal of cellular debris as needed. This filter may be microfabricated between the cell lysis module and the subsequent module, as shown in Fig. 1B where filter 200 is between handling well 40 and detection well 30, to enable the removal of the lysed cell membrane and other cellular debris components; examples of suitable filters are shown in EP 0 637 998 B1, incorporated by reference.

The paragraph beginning on page 38, line 16 was amended as follows:

In this and other embodiments, a thermal module may be used, that is either part of the reaction chamber or separate but can be brought into spatial proximity to the reaction module. The thermal module can include both heating and/or cooling capability. Suitable thermal modules are described in U.S. Patent Nos. 5,498,392 and 5,587,128 and WO 97/16561, incorporated by reference, and may comprise electrical resistance heaters, such as heater 250 in Fig. 1D, pulsed lasers or other sources of electromagnetic energy directed to the reaction chamber. It should also be noted that when heating elements are used, it may be desirable to have the reaction chamber be relatively shallow, to facilitate heat transfer; see U.S. Patent No. 5,587,128.

The paragraph beginning on page 39, line 5 was amended as follows:

In a preferred embodiment, the pumps are contained on the device itself. These pumps are generally electrode based pumps; that is, the application of electric fields can be used to move both charged particles and bulk solvent, depending on the composition of the sample and of the device. Suitable on chip pumps include, but are not limited to, electroosmotic (EO) pumps and electrohydrodynamic (EHD) pumps; these electrode based pumps have sometimes been referred to in the art as "electrokinetic (EK) pumps". All of these pumps rely on configurations of electrodes placed along a flow channel, such as pump 260 in Fig. 1A comprising electrodes 261 and 262, to

result in the pumping of the fluids comprising the sample components. As is described in the art, the configurations for each of these electrode based pumps are slightly different; for example, the effectiveness of an EHD pump depends on the spacing between the two electrodes, with the closer together they are, the smaller the voltage required to be applied to effect fluid flow. Alternatively, for EO pumps, the spampcing between the electrodes should be larger, with up to one-half the length of the channel in which fluids are being moved, since the electrode are only involved in applying force, and not, as in EHD, in creating charges on which the force will act.

The paragraph beginning on page 40, line 28 was amended as follows:

In a preferred embodiment, the devices of the invention include at least one fluid valve that can control the flow of fluid into or out of a module of the device, such as valve 280 in Fig. 1A, or divert the flow into one or more channels. A variety of valves are known in the art. For example, in one embodiment, the valve may comprise a capillary barrier, as generally described in PCT US97/07880, incorporated by reference. In this embodiment, the channel opens into a larger space designed to favor the formation of an energy minimizing liquid surface such as a meniscus at the opening. Preferably, capillary barriers include a dam that raises the vertical height of the channel immediated before the opening into a larger space such a chamber. In addition, as described in U.S. Patent No. 5,858,195, incorporated herein by reference, a type of "virtual valve" can be used.

The paragraph beginning on page 43, line 16 was amended as follows:

The detection electrode, such as electrode 35 in Fig. 2, comprises a self-assembled monolayer (SAM), such as monolayer 100 comprising conductive oligomers. By "monolayer" or "self-assembled monolayer" or "SAM" herein is meant a relatively ordered assembly of molecules spontaneously chemisorbed on a surface, in which the molecules are oriented approximately parallel to each other and roughly perpendicular to the surface. Each of the molecules includes a functional group that adheres to the surface, and a portion that interacts with neighboring molecules in the monolayer to form the relatively ordered array. A "mixed" monolayer comprises a heterogeneous monolayer, that is, where at least two different molecules make up the monolayer. The SAM may comprise conductive oligomers alone, or a mixture of conductive oligomers and insulators. As outlined herein, the efficiency of target analyte binding (for example, oligonucleotide hybridization) may increase when the analyte is at a distance from the electrode. Similarly, non-specific binding of biomolecules, including the target analytes, to an electrode is generally reduced when a monolayer is present.

Thus, a monolayer facilitates the maintenance of the analyte away from the electrode surface. In addition, a monolayer serves to keep charged species away from the surface of the electrode. Thus, this layer helps to prevent electrical contact between the electrodes and the ETMs, or between the electrode and charged species within the solvent. Such contact can result in a direct "short circuit" or an indirect short circuit via charged species which may be present in the sample. Accordingly, the monolayer is preferably tightly packed in a uniform layer on the electrode surface, such that a minimum of "holes" exist. The monolayer thus serves as a physical barrier to block solvent accesibility to the electrode.

The paragraph beginning on page 57, line 17 was amended as follows:

In a preferred embodiment, the detection electrode, such as electrode 35 in Fig. 2, further comprises a capture binding ligand, such as ligand 120 in Fig. 2, preferably covalently attached. In general, for most of the "mechanism-2" embodiments described herein, there are at least two binding ligands used per target analyte molecule; a "capture" or "anchor" binding ligand (also referred to herein as a "capture probe", particularly in reference to a nucleic acid binding ligand) that is attached to the detection electrode as described herein, and a soluble binding ligand, that binds independently to the target analyte, and either directly or indirectly comprises at least one ETM.

IN THE CLAIMS

Claims 36, 45, and 52 were amended as follows:

36. (Amended) A microfluidic device for the detection of a target analyte in a fluid sample comprising:

a) a solid support member;

b) a sample handling module including a sample handling well formed in said support member to receive and store said sample;

c) a sample inlet port to said microfluidic device;

d) a first microchannel formed in said support member and fluid coupled to and extending between said sample handling well and said sample inlet port;

e) ~~a detection module including~~ a detection well formed in said support member and a detection electrode positioned in said detection well, said detection electrode being provided with a self-assembled monolayer; and a binding ligand; and,

f) a second microchannel formed in said support member and extending between said sample handling well and said detection well for the flow of said fluid sample there between.

45. (Amended) A device according to claim 36, and a reaction module ~~including a reaction well~~ formed in said support member, wherein an additional microchannel connects the reaction module to said sample handling well ~~module~~ and a further microchannel connects the reaction well ~~module~~ to said detection module.

52. (Amended) A device according to claim ~~50~~36, further comprising ~~wherein said means for holding said sample is~~ a valve ~~means disposed of within said microfluidic device~~.

Claims 40-44, 48, and 51 were cancelled without prejudice or disclaimer.

Appendix A: Pending Claims

36. (Amended) A microfluidic device for the detection of a target analyte in a fluid sample comprising:

a) a solid support member;

b) a sample handling module including a sample handling well formed in said support member to receive and store said sample;

c) a sample inlet port to said microfluidic device;

d) a first microchannel formed in said support member and fluid coupled to and extending between said sample handling well and said sample inlet port;

e) a detection well formed in said support member and a detection electrode positioned in said detection well, said detection electrode being provided with a self-assembled monolayer; and a binding ligand; and,

f) a second microchannel formed in said support member and extending between said sample handling well and said detection well for the flow of said fluid sample there between.

37. The device of claim 36, and a reagent positioned in said sample handling well:

38. The device of claim 37 wherein said reagent comprises a cell lysing agent.

39. The device of claim 36, and a filter adapted for the removal of cellular debris, said filter positioned between said sample handling well and said second microchannel.

45. (Amended) A device according to claim 36, and a reaction module formed in said support member, wherein an additional microchannel connects the reaction module to said sample handling well and a further microchannel connects the reaction well to said detection module.

46. A device according to claim 45, and reagents for nucleic acid amplification positioned in said reaction module.

47 A device according to claim 45, and an electrical resistance heater positioned in said reaction module.

49. A device according to claim 36, and a means for inducing flow of a sample through said microfluidic device.

50. A device according to claim 48 wherein said means for inducing flow comprises a pump.

52. (Amended) A device according to claim 36, further comprising a valve.

53. A device according to claim 36 wherein said binding ligand is a nucleic acid.